EDITORIAL COMMENT

Comparison of Crinone 8% Intravaginal Gel and Intramuscular Progesterone for Luteal Support in *In Vitro* Fertilization

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In their study, Ho et al[1] report that using vaginal progesterone gel twice daily for luteal support resulted in better pregnancy outcomes than intramuscular progesterone. Vaginal progesterone gel seemed to offer more "targeted" delivery of progesterone to the uterus and improved endometrial receptivity. The authors also concluded that for patients with serum estradiol levels on the day of human chorionic gonadotropin greater than 5,000 pg/mL, vaginal gel still resulted in better ongoing pregnancy and implantation rates.

In vitro fertilization (IVF) is a relatively new field in medicine. Most of the individual studies in luteal phase supplementation in IVF, excluding meta-analyses which have their own limitations, lack adequate power analysis to determine statistical significance, especially if the study is a negative one.

Nevertheless, this study addressed the following questions that are still in need of scientific investigation.

1. Should the dose of progesterone be dependent on peak estradiol level, the type of stimulation protocol used, the age or the body weight of the patient?
2. What is the optimal dose of progesterone, both for vaginal gel and intramuscularly administrated preparations (IMP)?
3. Would the protocol benefit from additional estradiol supplementation, what is the optimal dose of estradiol, and when should it start and end?
4. When is the optimal time to start progesterone supplementation? Before embryo transfer? And when should it end?

The Importance of Progesterone in Early Pregnancy

A classic series of studies conducted more than 3 decades ago demonstrated that progesterone secretion by the corpus luteum (CL) is an absolute necessity for the success of early human pregnancy. The success of early pregnancy depends on progesterone that is primarily from the corpus luteum before 7 weeks of gestation, almost entirely from the trophoblast after 9 weeks of gestation, and from both sources to varying extents in the time between, which is known as the luteal-placental shift. There are no reliable methods for diagnosing progesterone deficiency during the luteal phase or early pregnancy. Serum progesterone concentrations vary widely during the mid and late luteal phases because progesterone secretion by the corpus luteum is pulsatile. Levels as low as 2.3 ng/mL and as high as 40.1 ng/mL have been observed within the relatively short interval of time spanning a single secretory pulse (60–90 minutes).[2] Single and even serial serum progesterone measurements have limited clinical utility and may not provide a truly accurate gauge of the quality of luteal function.

Role of the Endometrium and Embryo in Human Implantation

The process of implantation requires a reciprocal interaction between blastocyst and endometrium,

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culminating in a small window of opportunity during which implantation can occur. Implantation itself is governed by an array of endocrine, paracrine and autocrine modulators of embryonic and maternal origin. Implantation failure is thought to occur as a consequence of impairment of embryo developmental potential and/or impairment of uterine receptivity and the embryo-uterine dialogue. Progesterone and estrogen are the dominant hormonal modulators of endometrial development. Both the epithelial and stromal compartments express progesterone and estrogen receptors, and the response depends on the levels of these receptors as well as on the concentration of the hormones themselves. Although progesterone and estrogen are the key modulators of endometrial maturation, their roles in this process are complex and sophisticated. Hormonal activity depends not only on the levels of progesterone, estrogen and their receptors, but also on the rates of progesterone and estrogen metabolism. The activities of progesterone and estrogen are also influenced by the effects of co-activators and repressors. Furthermore, both hormones regulate the expression of numerous endometrial proteins. In addition to progesterone and estrogen, a number of other endocrinologic factors are known to mediate endometrial function.[3] By understanding the activity and function of the hormones and factors involved in this dialogue, it may be possible to use them as predictors of endometrial receptivity or embryo quality to maximize implantation rates in hormonally stimulated assisted reproductive technology (ART) cycles.

Rationale for Hormonal Supplementation with Progesterone in Stimulated IVF Cycles

In stimulated cycles typical of IVF therapy, the luteal phase is different from the natural one in 2 important ways. First, since ovarian stimulation produces multiple corpora lutea, the levels of both estradiol and progesterone in the early part of the luteal phase are supraphysiological. Second, and perhaps more importantly, the duration of ovarian steroid production in stimulated cycles is usually shorter than normal by 1–3 days. This truncated luteal phase has been noted since the earliest days of IVF and created concern that an early menses might prevent successful implantation since menses were on occasion observed to occur as early as 10 days after egg retrieval.[4]

In stimulated IVF cycles, the use of gonadotropin-releasing hormone (GnRH) agonists and the removal of granulosa cells during aspiration of the oocyte can lead to a relative progesterone deficit and inappropriate preparation of the endometrium for embryo implantation and survival of the pregnancy. The use of GnRH agonists in ovarian stimulation, which prevents a premature surge of luteinizing hormone (LH), ultimately leads to suppression of the pituitary gland, thereby blocking the secretion of LH for at least 10 days following the last applied GnRH dose, as well as the pulsatile secretion of progesterone. In addition, high levels of estrogen observed during stimulated cycles result in an inhibitory effect on the implantation of human embryos. The use of pharmaceutical luteal support to reach the physiologic ratio of estrogen to progesterone could only be beneficial.[5]

Timing of Luteal Support and When It Should End

Mochtar et al, in a 3-armed randomized prospective study with patients on a GnRH agonist suppression protocol, reported no significant differences in ongoing pregnancy rate when micronized vaginal progesterone was started the day after human chorionic gonadotropin (hCG) administration, the day of oocyte retrieval, or the day of embryo transfer. We can conclude that most IVF clinicians start supplementation after oocyte retrieval and before embryo transfer, but the optimal time, if there is one, is still not known.[6]

Andersen et al, in a prospective and randomized study, substantiated the other studies and reported no difference in the delivery rate between pregnant patients who discontinued progesterone when the patient had a positive pregnancy test and those who continued it until 7 weeks of gestation. All of the prior studies included a relatively large number (180–400) of patients. As such, we can conclude that there is no strong evidence in the literature that supports continuation of supplementation beyond the first positive hCG result.[7]

However, most clinicians empirically continue supplementation through to about 10 weeks of gestation (or 8 weeks from egg retrieval).

Route of Progesterone Administration for Luteal Support

Possible routes of progesterone delivery include transdermal, oral, intramuscular, transvaginal, sublingual, nasal, and rectal. Only 3 routes of support—oral, intramuscular, and transvaginal—have been widely used, and only 2—intramuscular and transvaginal—are satisfactory methods at this time.

There is special need for luteal support in controlled ovarian hyperstimulation induced for IVF–embryo transfer (IVF-ET), particularly when GnRH agonists are used. This support can be achieved either by repeated hCG injections or by progesterone supplementation. The latter option has been universally preferred since it has become evident that hCG injections increase the risk of frank ovarian hyperstimulation syndrome (OHSS).

Progesterone administered orally is extensively degraded by hepatic first-pass metabolism and the serum level typically returns to baseline level by 6 hours, which makes this route inefficient for luteal support. Therefore, progesterone should be administered only non-orally to support endometrial receptivity in infertility treatments. Although intramuscular administration is effective, clinicians have pursued a vaginal alternative in an attempt to avoid painful intramuscular injections.

In the US, the first FDA-approved system for pregnancy support was Crinone 8% (Fleet Laboratories Ltd., Hertfordshire, UK). It is a bioadhesive vaginal gel that contains 90 mg of micronized progesterone in an emulsion system designed to adhere to the vaginal mucosa and thus achieve controlled and sustained delivery. The advantages of Crinone over other vaginal therapies are a longer half-life and lower patient-to-patient variability in absorption. Crinone 8% applied once to twice a day provides progesterone directly to the endometrium through a first-uterine-pass effect. The serum level remains elevated for up to 48 hours. Further, Jobanputra et al, in a donor-egg IVF study, showed that 100% "in-phase" endometrial biopsies, reassuring pregnancy rates (46–48% *vs.* 41%) and miscarriage rates (14–33% *vs.* 25%) were seen at both the twice and once-daily dosing levels compared to intramuscular therapy. Pregnancy rates were as high with vaginal as with intramuscular therapy. There were no significant differences in clinical pregnancy and implantation rate using twice-daily Crinone or once-daily Crinone.[8] Khan et al, in a case-matched comparison of Crinone 8% and IMP demonstrated similar pregnancy, miscarriage, and live birth rates.[9] However, there are other studies that have shown that women who received IMP had higher ongoing pregnancy and live birth rates per transfer.[10]

Ho et al[1] found that the vaginal gel group compared with the IMP group had lower mid-luteal serum progesterone levels but higher implantation rate (32.5% *vs.* 18.5%) and ongoing pregnancy rate (55.2% *vs.* 32.5%). However, the retrospective nature of the study, with its associated biases, as well as the potential impact of other confounding variables (e.g. presence or absence of uterine factors, embryo scorings, etc. was equal across studied groups) limit their outcomes. The authors should provide results for ongoing pregnancy—defined as a viable pregnancy confirmed at 20 weeks of gestation, rather than just a viable fetus at 12 weeks of gestation, because the occurrence of a few early pregnancy losses might have significantly altered the reported outcomes.

The Optimal Dose of Progesterone

Supplementation of the luteal phase in IVF started empirically, and unfortunately, the data are limited with regard to the best dose. Few randomized trials have been performed to compare dosages and formulations. No differences were observed in clinical pregnancy rates.[8] As such, there is definitely a need for more randomized controlled trials to assess the effectiveness of different doses for the different progesterone formulations. However, Ho et al, in their retrospective study, only compared twice-daily Crinone with IMP.

Addition of Estradiol to Progesterone in IVF Cycle

The implantation process depends on the quality of the endometrium, which is affected by both estradiol and progesterone. During the follicular phase, it is mainly dependent on estradiol. The role of estradiol during the luteal phase is unclear. However, in IVF cycles, the levels of estradiol and progesterone drop in the mid to late luteal phase.

Farhi et al evaluated the effect of adding 2 mg of estradiol orally twice a day to 50 mg intramuscular injection of progesterone and 50 mg vaginal progesterone twice a day. The estradiol supplementation was started on day 7 after embryo transfer. The study included women who were felt to be at risk of OHSS and who were not candidates for hCG luteal phase supplementation (estradiol > 2,500 pg/mL on the day of hCG trigger). A higher pregnancy rate was observed in women who received estradiol and long GnRH agonist protocols (39.6% *vs.* 25.6%, $p < 0.05$).[11]

Lukaszuk et al conducted a randomized prospective study on the dose of micronized estradiol needed in patients on the long GnRH agonist protocol. Patients were randomized to receive no estradiol, 2 mg, or 6 mg of micronized estradiol, in addition to 200 mg three times daily of vaginal micronized progesterone. In the trial, estradiol was started on the day of oocyte retrieval. The addition of estradiol during the luteal

phase resulted in an increase in implantation and pregnancy rates. The pregnancy rate was 51.3% in women who received the high estradiol dose (6 mg), whereas it was 32.8% in those on the 2 mg dose, and only 23.1% in the no estradiol group. Multiple pregnancies were also statistically significantly higher in women who received estradiol. The rates of spontaneous abortions and ectopic pregnancies were similar in all 3 groups.[12]

The cycles were suppressed with a mid-luteal GnRH agonist protocol. Similarly, Tay and Lenton[13] did not find an advantage in the clinical pregnancy rate when oral estradiol valerate (2 mg) and 400 mg of micronized progesterone applied vaginally were compared with progesterone alone. In 1 prospective study, 600 mg of micronized vaginal progesterone once daily was compared with the combination of vaginal progesterone and 6 mg of estradiol valerate. The clinical pregnancy rates were similar.[14]

In a more recent trial in which a GnRH antagonist was used, patients were randomized to receive progesterone alone or progesterone and estradiol during the luteal phase. All women received 200 mg of micronized progesterone vaginally 3 times daily. One group also received 2 mg of estradiol valerate orally twice a day. Both progesterone and estradiol were started the day after oocyte retrieval. The endocrine profile (follicle-stimulating hormone, LH, estradiol, progesterone) was similar in both groups, and the investigators concluded that the addition of estradiol in GnRH antagonist cycles was unlikely to affect pregnancy rates.[15]

Supplementing with Progesterone Alone and/or hCG in IVF Cycles

Luteal support is most commonly provided by treatment with supplemental progesterone but can also be achieved effectively by the administration of exogenous hCG. In IVF cycles involving treatment with a long-acting GnRH agonist, hCG stimulation of luteal function and progesterone supplementation have similar effectiveness. In an analysis of combined data from 6 clinical trials involving a total of 1,038 women, the ongoing pregnancy rate per embryo transfer in cycles supplemented directly with progesterone was not significantly different from that in cycles supplemented with hCG (odds ratio, 0.94; 95% confidence interval, 0.70–1.27).[8] However, the risk for OHSS was significantly lower in women who received progesterone supplementation than for those who were treated with hCG (odds ratio, 0.46; 95% confidence interval, 0.26–0.81).[16]

Summary and Recommendations

Luteal-phase supplementation in IVF stimulated cycles is a well-established practice that will continue in the future. Success rates are similar with intramuscular and vaginal administration, with patient preference for the vaginal route. Pregnancy rates are also similar for different forms of vaginal progesterone.

Currently, there is no reliable method for the specific diagnosis of progesterone deficiency during the luteal phase of the menstrual cycle or early pregnancy.

In IVF cycles involving downregulation with a long-acting GnRH agonist, progesterone supplementation (50 mg/day administered intramuscularly, or Crinone 8%, 90 mg/day, administered vaginally) yields significantly higher pregnancy rates when compared with treatment with placebo or no treatment.

Luteal-phase supplementation with hCG is associated with greater risk of OHSS compared with supplementation with progesterone.

Luteal-phase supplementation in IVF stimulated cycles is considered to be an essential requirement for optimal success.

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